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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/374,586	08/13/99	PINSKY D	59167/JPW/JM

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EXAMINER	
STROUP,C	
ART UNIT	**PAPER NUMBER**
1633	8

DATE MAILED: 05/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/374,586	Pinsky DJ
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-26 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-26 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's arguments in Paper 5, filed 3/6/00, regarding the restriction requirement issued in Paper 4, filed 1/27/00, have been taken into consideration and found to be persuasive. Therefore, the restriction requirement is withdrawn and claims 1-26 are pending in the current application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-16 and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claimed invention is to a method of treating or preventing stroke in a subject wherein the subject is susceptible to intracranial hemorrhaging, comprising the administering of an active fragment of CD39, such as amino acids 1-50 of SEQ ID NO:2 or amino acids 20-80 of SEQ ID NO: 1, wherein the fragment acts to inhibit adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphosphate catabolism in the subject. Said fragment may be a mutated or a truncated form of CD39 polypeptide, or a soluble form of CD39 produced recombinantly with a IL-2 leader sequence and lacking a transmembrane domain.

The specification discloses that SEQ ID NO: 1 is the coding sequence for CD39 and SEQ ID NO: 2 is a variant of CD39 (pg 9, lines 3-5). The specification then provides a general disclosure on the composition of other variants, such as that they may have substitutions, deletions, or insertions which do not abolish the biological activity associated with CD39 and which may have increased potency, bioavailability, stability or decreased toxicity (pg 9, line 28-pg 12, line 10). The specification provides an exemplification in which transgenic mice homologously deficient in CD39 were produced via embryonic stem cell therapy, wherein said mice appeared to exhibit a latent prothrombotic phenotype and diminished blood flow following perfusion as a result of induction of focal cerebral ischemia (pg 32, lines 7-16), but they did not exhibit a change in hematologic profiles, platelet counts, hemoglobin levels, white blood cell counts and PT/PTT (pg 28, liens 10-13). Said mice were intravenously administered a soluble form of CD39 generated by removing the NH-2 and COOH terminal transmembrane coding regions and produced recombinantly with an IL-2 promoter (pg 21,lines 15-23), and exhibited postischemic flows similar to the controls, and were thus ruled to be protected from stroke as shown by their markedly diminished infarct volumes at 24 hours (Figure 6B, pg 28, lines 1-33). The specification also discloses that the administration of CD39 pre and post stroke onset is dose dependent in reducing cerebral infarct volumes, neurological deficit and mortality (pg 29, lines 33-35).

In the various exemplifications provided in the specification, only the polypeptide of SEQ ID NO: 2 is utilized. The specification does not indicate what distinguishing feature of any other fragment of CD39 must exist for utilization in the claimed invention, other than that it acts to inhibit adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphosphate catabolism in the subject or that it reduces cerebral infarct volumes, neurological deficit and mortality. Thus, the scope of the claims include numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted, yet the specification does not provide guidance as to specific changes to make. Structural features that could distinguish CD39 fragments in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify

the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, such as which specific protein domains confer the ability to inhibit platelet aggregation, and because the genus is highly variant, the ability to inhibit adenosine diphosphate-mediated platelet aggregation by increasing adenosine diphosphate catabolism in the subject is insufficient to describe the genus. One of skill in the art would reasonable conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

4. Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse homozygous deletion in CD39 and use in identifying compounds which inhibit platelet aggregation via the ADP pathway; and the use of soluble CD39 in the treatment and prevention of thrombotic and ischemic disorders in mice and BIBU52 in rhesus and marmoset monkeys (Guth et al, abstract), does not reasonably provide enablement for the use of any CD39 fragment or full-length CD39 (SEQ ID NO:1) in treating or preventing stroke; or the use of an animal model of in testing for compounds which inhibit platelet aggregation via any pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

As stated in the preceding section, the specification fails to disclose the identity of any CD39 fragment, other than the exemplified SEQ ID NO:2, with the ability to inhibit platelet aggregation by increasing adenosine diphosphate catabolism or that the full length CD39 (SEQ ID NO: 1) demonstrates said ability. And although the specification provides a general disclosure on the methods of generating additional CD39 variants (pg 8, line 25-pg 12, line 10), said disclosure does not provide specific details on the composition of a fragment which is necessary to inhibit platelet aggregation. Therefore, in the absence of teachings disclosing the ability of the full length CD39 or any variant other than the soluble form of CD39 (claim 5) to inhibit platelet aggregation or ADPase activity in vivo, or even to maintain its biological activity in vivo for long periods of time following i.v. administration (see Gayle et al, pg 1853, col 1, "Pharmacokinetic analysis"), the artisan would be required to practice undue experimentation to utilize any other fragment of CD39 such that any therapeutic outcome could occur.

The specification also fails to provide an enabling disclosure for a method of treatment or prevention of any stroke in any subject other than the exemplified mouse. The Applicant asserts on page 25, lines 25-26, of the specification that the exemplified mice are an art accepted model for stroke injury and could therefore be used to analyze the occurrence of latent prothrombotic phenotype and the effect of administering CD39 to inhibit platelet aggregation in vivo (pg 34, lines 17-20). It is noted that none of the teachings incorporated by reference into the specification to support the use of the mouse ischemic model, such as reference number 2, 3, or 25, have been provided to the Examiner. As such, they have not been taken into consideration. Additionally, it was well known in the art at the time of the invention that proteins involved in thrombosis displayed different levels of activity between specifies. For example, Fay et al (*Arteriosclerosis, Thrombosis, and Vascular Biology*, October 1996, 16(10): 1277-1284) demonstrated that porcine plasminogen activator inhibitor-1 (PAI-1) displayed a significantly higher level of activity than human PAI-1. Therefore, one of skill in the art would be required to practice undue experimentation to

extrapolate the method of administering the soluble form of CD39 exemplified by the specification, to a non-mouse subject, such as a human, such that a predictable level of treatment or prevention of stroke could occur.

Lastly, the specification fails to provide an enabling disclosure for the use of an animal model to test for compounds which inhibit platelet aggregation by inhibiting ADP catabolism by measuring said compounds effect on all types of platelet deposition (claim 17c). Platelet aggregation during thrombosis is induced by collagen, ADP, and a thrombin receptor-activating peptide (Guth et al, abstract). In as much as soluble CD39 has been disclosed by the art to be an ADPase, the claimed invention is not enabled for testing compounds which are not previously known to be ADPase's because the artisan would not be able to discern if any platelet aggregation resulting from use of a test compound acted via collagen or thrombin receptor-activating peptide pathway or ADPase pathway. The specification does not teach the manner of blocking the collagen or thrombin receptor-activating pathways in the animal model to ensure that any effect the compound had on the inhibit of platelet aggregation was through the ADPase pathway. The specification also does not disclose assays to test specifically for inhibition of platelet aggregation via the ADPase pathway versus via the inhibition of the collagen or thrombin receptor-activating pathways. Therefore, one of skill in the art would be required to practice additional and undue experimentation to identify the pathway by which any compound might inhibit platelet aggregation in the claimed transgenic CD39 $^{+}$.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been

obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 17 and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guth et al (8/97) in view of Gayle et al (1998).

Applicant's claimed invention is to a method for determining whether a compound, such as soluble CD39, inhibits platelet aggregation by increasing ADP catabolism so as to treat or prevent thrombotic or ischemic disorders comprising utilizing an animal model of said disorders and measuring the platelet and fibrin deposition, wherein the compound may be administered before, during, or after the onset of stroke.

Guth et al disclose the use of three different animal models of recurrent arterial thrombus formation to test the efficacy of a compound, e.g. BIBU52 to inhibit ADP driven platelet aggregation in rhesus and marmoset monkeys. Guth et al does not disclose the use of CD39.

Gayle et al disclose a recombinant soluble form of CD39 and demonstrates its antithrombotic activity in vitro by catabolizing ADP and resulting in the inhibition of platelet aggregation, and that it remained biologically active in vivo while circulating for prolonged periods of time. (full article, abstract, Figure 1; pg 1858, col. 2, para. 4).

In light of Guth et al and Gayle et al, it would have been obvious to one of ordinary skill in the art to utilize an animal model of thrombosis to test for the effect of a potential therapeutic compound on inhibiting ADP driven platelet aggregation. One would be motivated to utilize the soluble CD39 as the test compound in said model because Gayle et al had demonstrated that it inhibited platelet aggregation in vitro by catabolizing ADP and that it remained biological active in vivo, thus displaying the potential to inhibit platelet aggregation in an animal under thrombotic conditions.

7. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guth et al (8/97) in view of Gayle et al (1998) as applied to claims 17 and 20-24 above, and further in view of Beaudoin et al (US Patent 5,798,241).

The invention includes the compound identified via the claimed animal model and a pharmaceutical composition comprising said compound to treat thrombotic or ischemic disorders, such as soluble CD39.

Guth et al disclose the use of three different animal models of recurrent arterial thrombus formation to test the efficacy of a compound, e.g. BIBU52 to inhibit ADP driven platelet aggregation in rhesus and marmoset monkeys. Guth et al does not disclose the use of CD39 or pharmaceutical compositions comprising such.

Gayle et al disclose a recombinant soluble form of CD39 and demonstrates its antithrombotic activity in vitro by catabolizing ADP and resulting in the inhibition of platelet aggregation, and that it remained biologically active in vivo while circulating for prolonged periods of time. (full article, abstract, Figure 1; pg 1858, col. 2, para. 4).

Beaudoin et al teach the use of a composition of comprising mammalian ATP diphosphohydrolase with a pharmaceutically acceptable carrier to reduce platelet aggregation and thrombogenicity (claim 5; col. 9, lines 34-37).

In light of Guth, Gayle, and Beaudoin et al it would have been obvious to one of ordinary skill in the art to utilize a compound identified from an animal model of thrombosis which displayed the activity of catabolizing ADP, such as an ATP-diphosphohydrolase, in a pharmaceutical composition to prevent platelet aggregation leading to thrombogenicity. One would also be motivated to use soluble CD39 in said composition because it had already been classified as an ATP-diphosphohydrolase exhibiting inhibition of platelet aggregation in vitro.

No claim is currently allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-0294.

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